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Sepsis-induced cardiomyopathy

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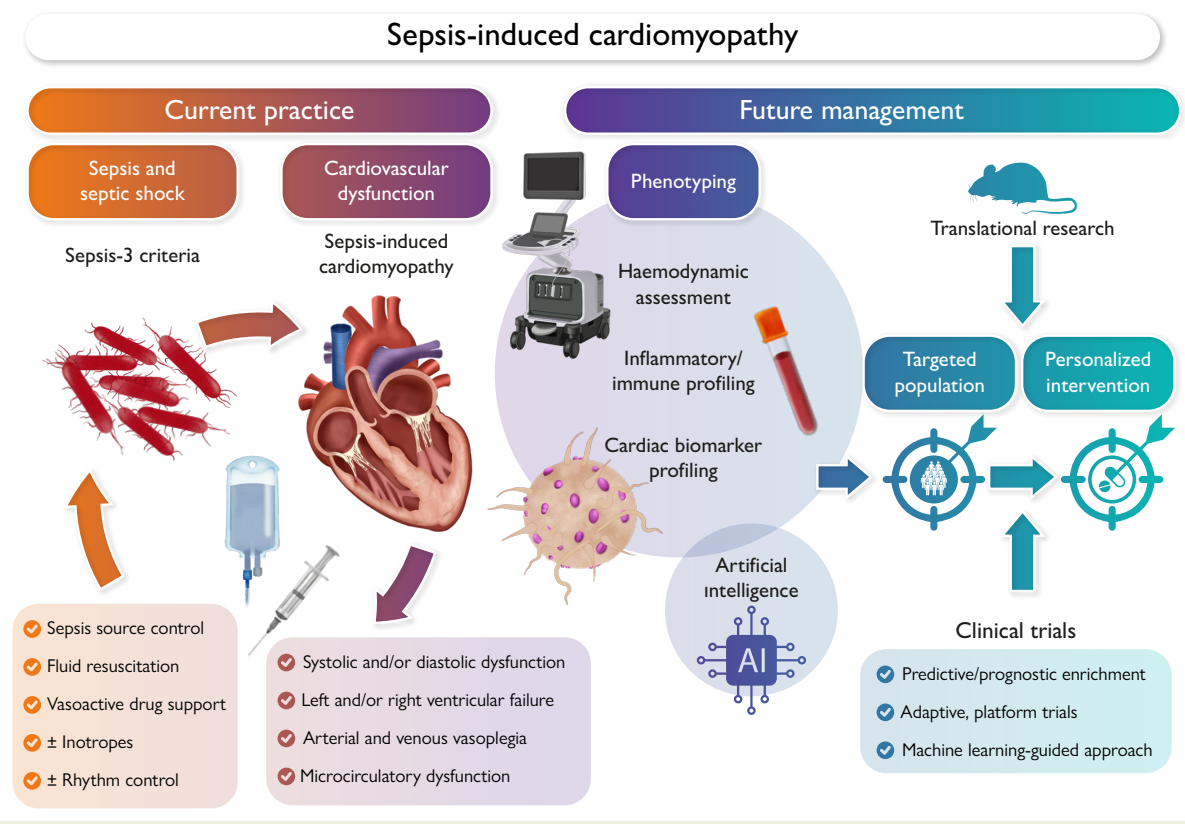
Graphical Abstract



Abstract

Sepsis remains the most common cause of death in critically ill patients worldwide and the most frequent non-cardiac disease diagnosed in the Coronary Care Unit. Myocardial dysfunction caused by sepsis, usually termed 'sepsis-induced cardiomyopathy' (SICM), is common and has long

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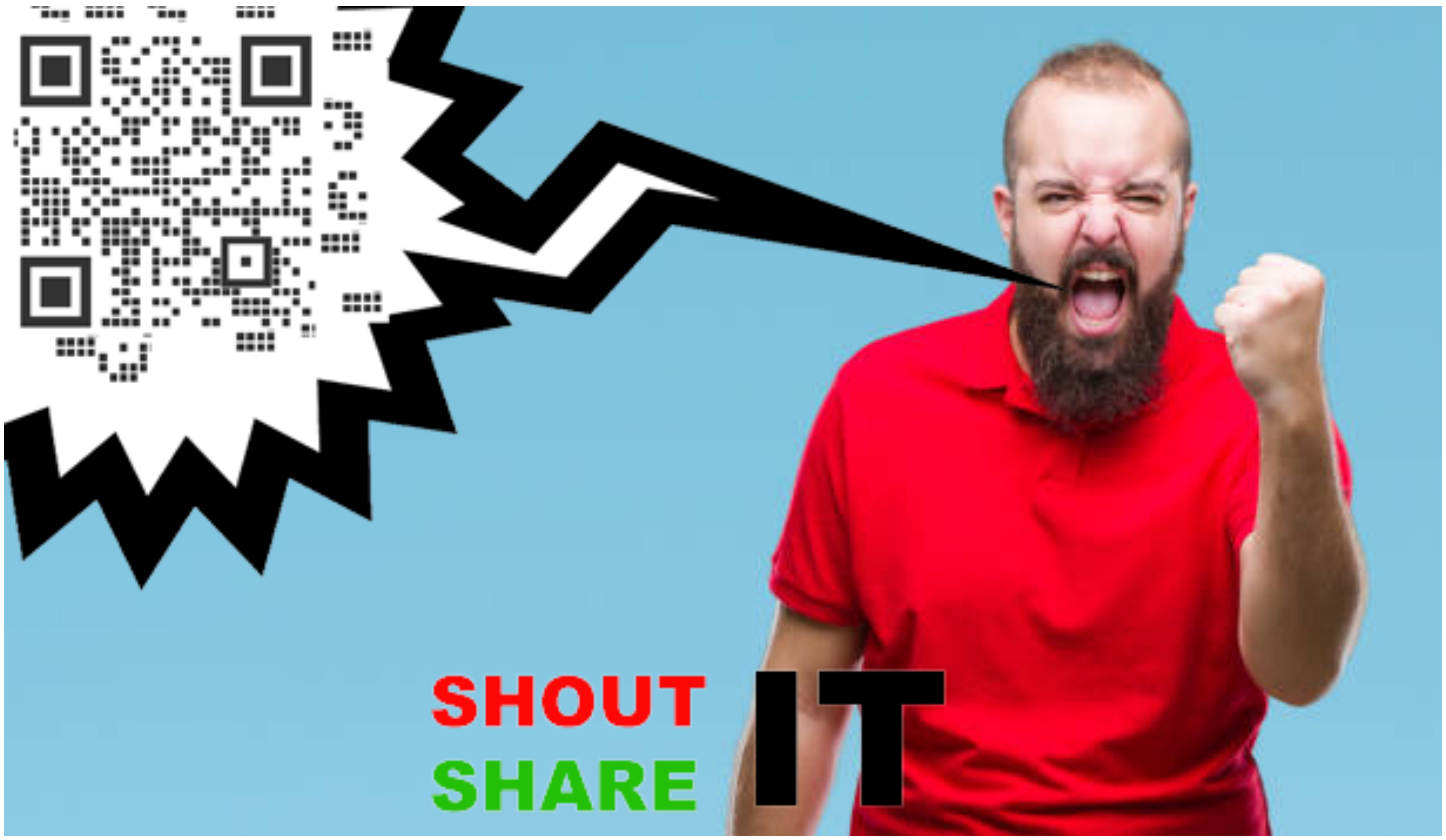
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been a subject of interest for intensivists and cardiologists. Despite the lack of a consensus definition, SICM is widely recognized as a reversible condition characterized by acute single or bi-ventricular systolic and/or diastolic dysfunction unrelated to coronary artery disease. While indications for monitoring and treating septic cardiomyopathy are directed towards restoring tissue perfusion, a better understanding of the course and implications of septic cardiomyopathy may help to optimize interventions and improve clinical outcomes. The present review aims to summarize current knowledge on the epidemiology, pathophysiology and clinical presentation of SICM, and to provide insights to aid clinicians in managing affected patients.

Keywords Sepsis-induced cardiomyopathy • New-onset LV systolic dysfunction • Sepsis

What are we talking about?

Mr L is a 52 year-old obese smoker who presents with severe hypotension, tachycardia, fever and productive cough. Chest X-ray reveals a lobar community-acquired pneumonia. An electrocardiogram demonstrates sinus tachycardia and a type I Brugada pattern. Echocardiography performed at admission shows a normal ejection fraction and a collapsed inferior vena cava. Despite fluid resuscitation and a norepinephrine infusion, hypotension (82/50 mmHg) persists with ongoing signs of tissue hypoperfusion including oliguria, increased capillary refill time and hyperlactatemia. Plasma high-sensitivity cardiac troponin I is raised at 92 ng/L (<14 ng/L). Echocardiography performed 4 h after intensive care unit admission now reveals severe left ventricular dysfunction.

Introduction

Myocardial dysfunction can develop alongside other organ dysfunctions during sepsis as a consequence of the dysregulated host response to an infectious trigger.[1] Sepsis-induced cardiomyopathy (SICM), or sepsis-induced myocardial dysfunction, denotes any type of myocardial dysfunction that is presumed transient and is triggered by the septic process itself.[2,3] Clinical presentation is variable as both systolic and diastolic function of either or both ventricles can be altered with an unpredictable degree of severity. The diagnosis of SICM may be particularly challenging in patients with known underlying heart disease.

The present review aims to summarize current knowledge on the epidemiology, pathophysiology and clinical presentation of SICM, and to provide insights to help clinicians manage such patients.

Epidemiology

Sepsis is '*a life-threatening condition that arises when the body's response to infection injures its own tissues*'.[4] Despite significant advances in its management, sepsis remains the most common cause of death in critically ill patients worldwide.[5] Sepsis is also the most frequent non-cardiac disease diagnosed in the Coronary Care Unit and is associated with increases in length of hospital stay, readmission and mortality.[6] Septic shock was initially identified as a life-threatening condition associated with high cardiac output and low systemic vascular resistance despite correction of hypovolemia.[7] It was considered that a continuum existed between an initial high flow state ('*warm shock*') and a subsequent hypodynamic state with low cardiac output and peripheral vasoconstriction ('*cold shock*').[8] Reversible sepsis-induced myocardial depression was first described in 1984 using radionuclide cineangiography in patients with septic shock, with survivors exhibiting a larger left ventricular (LV) cavity and lower LV ejection fraction (EF) compared with non-survivors.[9] In 1990, reversible myocardial depression was confirmed in survivors of septic shock using echocardiography; this was ascribed to systolic dysfunction affecting both ventricles.[10] In contrast to the initial hypothesis,[8] these pioneering studies showed that cardiac dysfunction could develop during the early phase of septic shock and was reversible with adequate management.[9,10]

Although there is no consensus definition, it is widely accepted that SICM manifests clinically as an acute single or bi-ventricular systolic and/or diastolic dysfunction unrelated to coronary disease.[3] The presence of new-onset LV systolic dysfunction in a septic patient with no alternative aetiology is widely recognized as the main diagnostic criterion of SICM.[2–4,11] Whether isolated LV diastolic dysfunction and isolated right ventricular (RV) dysfunction should be part of the definition of SICM is currently under debate.[11,12] Irrespective of its clinical presentation, SICM is typically reversible with control of sepsis.[2,3,11,12]

The literature reports a variable incidence of new-onset LV and RV systolic dysfunction depending on the population under study (e.g. sepsis vs. septic shock), imaging modality used for diagnosis, diagnostic criteria applied, timing of assessment, and initial resuscitation (e.g. volume of fluid loading, vasopressor support, invasive mechanical ventilation). When assessing patients with septic shock using echocardiography within 24 h following intensive care unit (ICU) admission, the reported prevalence of SICM defined by a decreased LVEF ranged between 18% and 60%.[3,11–17] Of note, SICM can develop up to 72 h after ICU admission in patients assessed daily with echocardiography.[16–19]

Studies assessing risk factors associated with the development of SICM are scarce and limited by their retrospective design and contradictory results.[20–22] One study assessing 210 patients hospitalized with sepsis or septic shock showed a higher prevalence of SICM in patients who were younger, male and with pre-existing heart failure.[21] Analysis of the MIMIC-III public database (38 605 patients, 3530 with sepsis) admitted to the ICU of Beth Israel Deaconess Medical Centre in Boston identified age, male sex, comorbidities, hemoglobin level, diabetes and mechanical ventilation use on the first day of ICU admission as risk factors for SICM.[22]

Pathophysiology

The pathophysiology of SICM involves a complex interaction of genetic, epigenetic, immunologic, environmental, iatrogenic and other factors (*Figure 1*).

The pathogen triggers an exaggerated inflammatory response with downstream production of multiple inflammatory mediators including cytokines, chemokines, adhesion molecules, eicosanoids, reactive oxygen, and nitrogen species that can affect the heart both directly and indirectly.[23–26]

Apart from direct myocardial injury, extrinsic factors can further compromise cardiac function. Hypotension resulting from

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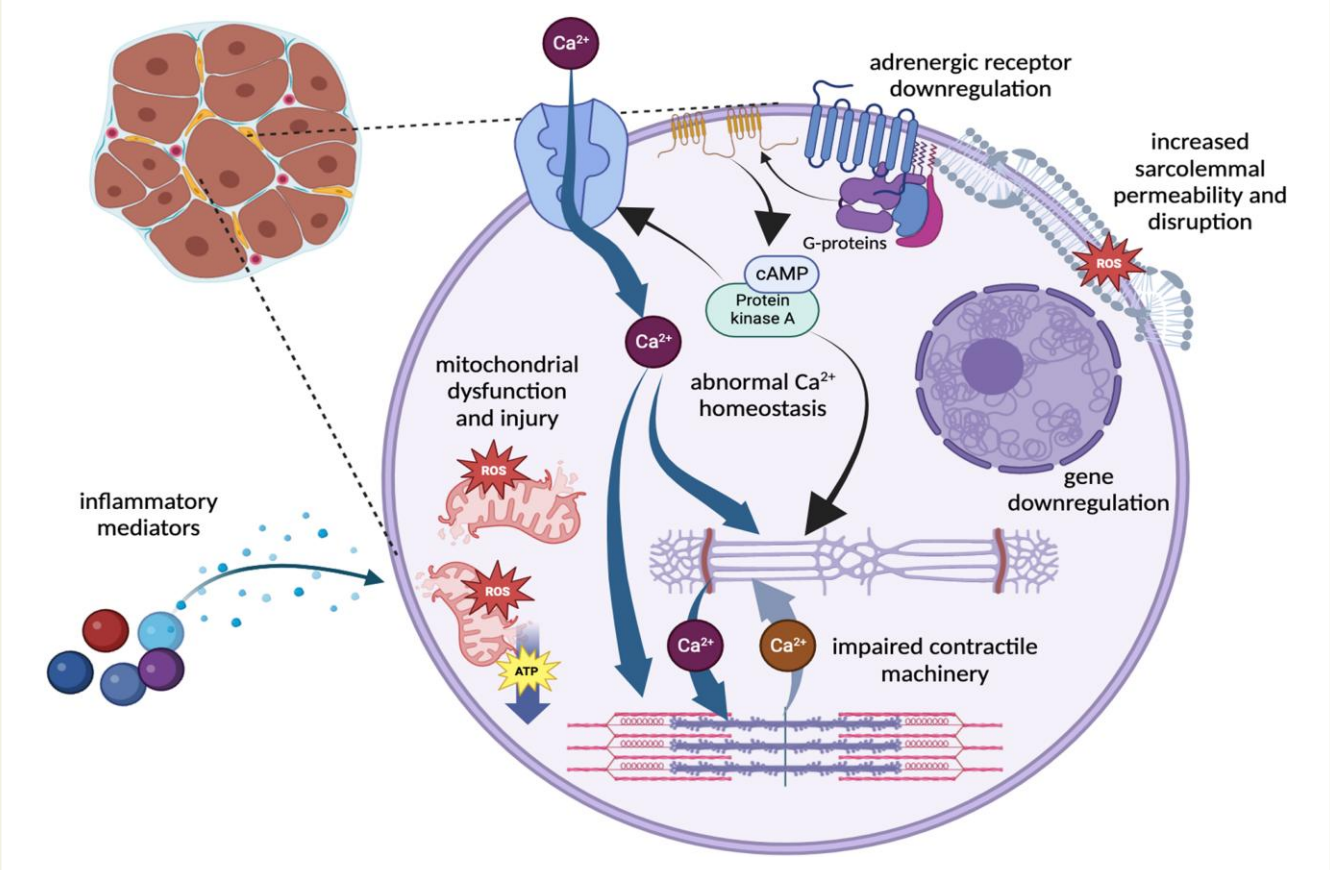

Figure 1 Pathophysiological pathways leading to SICM. ATP, adenosine triphosphate; cAMP, cyclic adenosine monophosphate; Ca^{2+}, calcium; G-proteins, guanine nucleotide-binding proteins; ROS, reactive oxygen species. Figure designed using BioRender

vasodilatation, loss of vascular tone, decreased catecholamine responsiveness and increased capillary leak can impact on circulating blood volume, flow and pressure with consequent effects on myocardial perfusion and performance. Notably, after resuscitation, myocardial perfusion is not compromised.[27,28] Iatrogenic harm may arise from volume overload and use of high-dose catecholamines. Characteristic histological features of catecholamine-induced myocardial damage including contraction band necrosis, myocytolysis, fibrosis, mononuclear infiltrates and interstitial edema correlated with catecholamine dose and duration.[29]

While laboratory models suggest cell death is a critical mechanism underlying SICM,[30] cardiomyocyte cell death is not a major feature in human sepsis. Apoptosis and necrosis were only infrequently seen at post-mortem[31] while reversibility, an important aspect of SICM, is often seen within days in both patients and animal models.[9,32,33] Nonetheless, despite minimal cell death, sepsis affects most, if not all, components of the cardiomyocyte, including the cell membrane, the contractile apparatus and mitochondria, at both functional and structural levels.

A hallmark of SICM is decreased responsiveness to adrenergic agents. This may relate to decreased expression, internalisation and/or reduced activity of sarcolemmal $ß_1$-adrenergic receptors, downstream perturbations of the adrenergic signalling pathway,[33,34] or upregulation of the negatively inotropic $ß_3$-adrenergic receptor.[35]

Increased sarcolemmal permeability related to oxidative damage to membrane lipids and proteins may be an early event leading to SICM.[36] This increased permeability may explain the hyperemia commonly seen in sepsis which prognosticates for poor outcome[37,38] and often exceeds levels seen with myocardial infarction. Troponin proteolysis, with leakage of cytoplasmic troponins, may cause reversible damage to the contractile machinery. A rapid fall in cardiomyocyte membrane cholesterol affects membrane fluidity[39] leading to increased permeability and decreased catecholamine responsiveness through effects on ß-adrenergic receptor membrane density and activity.[40]

Sepsis alters cardiomyocyte calcium trafficking, reducing contractility through effects on sarcolemmal depolarization and suppression of calcium currents through L-type voltage-gated calcium channels and ryanodine receptors.[41–43] The density of these calcium channels and receptors also decreases,[41–45] as does calcium uptake into the sarcoplasmic reticulum affecting lusitropy.[45] In addition there is down-regulation of cardiac contractile proteins[46] and reduced myofilament calcium sensitivity, often despite increased levels of intracellular calcium.[47,48] Recovery of cardiac contractility is associated with enhanced intracellular calcium handling, suggesting an active recovery process that includes sarcoplasmic reticulum calcium pump activation, phospholamban down-regulation, and sodium/calcium exchange inhibition.[47–52]

Mitochondrial abnormalities are frequently described, affecting oxidative phosphorylation, redox status with increased uncoupling, and mitochondrial membrane potential with consequent falls in ATP generation and increased ROS production.[53] These abnormalities are accompanied by significant changes in mitochondrial morphology,[33,54,55]

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calcium homeostasis[56] and dynamics such as fission, fusion, mitophagy and biogenesis.[53,57,58]

Apart from their impact on mitochondrial dysfunction, oxidative and nitrosative stress also impacts on sarcomeres and other organelles.[58–61] Multiple studies report a strong association between the extent of oxidative damage and the degree of cardiac dysfunction.[53]

Finally, an interesting phenomenon described in sepsis is myocardial hibernation with metabolic reprogramming.[53,62,63] This adaptive down-regulation of oxidative metabolism and function protects both mitochondria and cells from oxidative damage by decreasing mitochondrial membrane potential and ROS production, but at the expense of cardiac contractility. By reducing energetic demands, ATP depletion is prevented, which would prevent irreversible injury and initiation of cell death pathways.[64]

Differences are seen between bacterial and viral causes of sepsis.[65] COVID-19 infection was associated with various cardiovascular manifestations such as arrhythmias, myocarditis, Takotsubo cardiomyopathy, thromboembolism and acute cor pulmonale (especially in the setting of mechanical ventilation).[66,67] Main cardiac pathological findings of COVID-19 disease were cardiac dilatation, necrosis, lymphocytic infiltration of the myocardium, and small coronary vessel microthrombosis.[68]

Main features differentiating SICM from other cardiomyopathies

In patients with SICM, mean LVEF approximates 40%.[15,16,18] This corresponds to the cut-off defining heart failure with reduced LVEF.[69,70] Specific characteristics can distinguish SICM-related LV systolic dysfunction from other acute cardiomyopathies encountered in critical illness, including adrenergic 'stress' cardiomyopathy (Takotsubo syndrome) and fulminant myocarditis (see ESM *S1*, Supplementary data online, *Table S1*).

First, LV filling pressure remains typically normal or low, irrespective of LV systolic function.[2,3] Although a pre-existing cardiomyopathy and high-volume fluid resuscitation can result in pulmonary venous congestion, the absence of elevated left filling pressures likely relates to an acute increase in LV compliance and the frequent presence of associated RV dysfunction.[2] While the initial descriptions of sepsis-induced LV dilatation were overestimated due to indirect calculations of end-diastolic volume by radionuclide ventriculography,[71] subsequent echocardiographic studies do confirm moderate LV cavity enlargement and associated LV systolic dysfunction in patients with septic shock.[15,72–74] LV end-diastolic volume usually remains within the normal range due to pericardial constraints.[15] Intravenous administration of endotoxin to healthy volunteers with subsequent fluid loading increased LV end-diastolic volume by ~15%–20% while, compared with controls, LVEF decreased to a lesser extent and the ratio of pulmonary capillary wedge pressure to LV end-diastolic volume increased to a lesser extent.[32] Taken together, these results indicate depressed intrinsic LV contraction and increased LV compliance. Sepsis-induced RV dysfunction leads to systemic venous congestion but this may protect the pulmonary circulation since such patients are fluid non-responders.[75] RV dysfunction can also mask associated LV failure.[2] In addition to an intrinsic contractility defect, increased afterload is a major component of sepsis-induced RV injury. Involvement of lung dysfunction as part of the septic process results in acute pulmonary hypertension. Infection is the origin of moderate-to-severe acute respiratory distress syndrome (ARDS) in up to three-quarters of cases.[76] In these patients, invasive mechanical ventilation represents an additional burden to RV ejection.[2]

Second, SICM develops early in the course of sepsis and rapidly recovers in survivors, usually within a few days (*Figure 2*), and irrespective of its severity.[14–16,74,77] Early hemodynamic assessment in the Emergency Department predominantly demonstrates hypovolemia (60%) and a hyperdynamic circulation due to marked vasoplegia (31%).[78] Nevertheless, early LV or RV failure is encountered in 18% and 13% of septic patients, respectively, after a median intravenous fluid load of only 1000 mL (IQR: 500;1500 mL).[78] In 10%–20% of patients admitted to the ICU for septic shock, LV systolic dysfunction may be absent at the time of first echocardiographic assessment and may only develop on Days 2–3.[14,16] Since LVEF is highly influenced by loading conditions, correction of both sepsis-induced hypovolemia and vasoplegia may unmask SICM.[3] Importantly, LVEF is closely related to LV afterload,[79] especially during septic shock.[14] Initially preserved ventriculo-arterial coupling, which maintains normal LVEF in the presence of marked arterial vasodilatation, may be rapidly hampered by restoration of vascular tone through vasopressors and infection source control. Overall, serial hemodynamic assessments and monitoring of therapeutic interventions allow changes of the cardiovascular phenotype to be identified during the acute phase of septic shock. This applies especially to LV and/or RV failure that may develop secondarily in response to unfavorable cardiac loading conditions.

Third, reversible LV diastolic dysfunction may also develop whether systolic function is depressed or not.[77] Depending on the criteria used, the prevalence of sepsis-associated LV diastolic dysfunction ranges from 20% to 57%.[80] The clinical consequences of LV diastolic dysfunction in septic patients remain unclear,[3] especially as baseline diastolic function is usually unknown.[80] Echocardiographic assessment of LV diastolic function is also challenging in these patients due to tachycardia, abrupt changes in loading conditions, ventricular and heart-lung interactions. Accordingly, current echocardiographic guidelines[81] may not be applicable to this specific population.[82,83]

Clinical evaluation

Hemodynamic instability, clinical signs of tissue hypoperfusion or any intolerance of ongoing therapy (e.g. fluid challenge, inotropes, ventilator settings) should trigger a prompt and detailed assessment to identify both the cause and the cardiovascular phenotype present at that time (*Figure 3*).[84] Non-clearance of biological markers suggestive of tissue dysoxia (e.g. lactate) should also trigger a careful hemodynamic evaluation, even in patients whose blood pressure has stabilized. Low values of mixed or central venous oxygen saturation are consistent with inadequate oxygen delivery relative to consumption; this should also prompt re-assessment of cardiac function (*Figure 3*). This biological marker, however, lacks sensitivity since tissue oxygen extraction is often impaired in sepsis.[85]

There are no diagnostic electrocardiographic findings specific for SICM. The most common rhythms are sinus tachycardia and atrial fibrillation.[85] Risk factors for new-onset atrial fibrillation are mainly associated with the acute sepsis event rather than those for community-acquired atrial fibrillation.[86] A fever-induced type I Brugada pattern may be erroneously interpreted as a myocardial ischemia-related ST elevation.[87]

No blood biomarker is diagnostic of SICM[88] Biomarkers indicating cardiomyocyte injury (troponin) or ventricular dysfunction (B-type natriuretic peptide) are frequently elevated in sepsis[89,90] and often rise with non-cardiac disease inflammatory conditions.[91] The magnitude of rise often relates to illness severity rather than the presence

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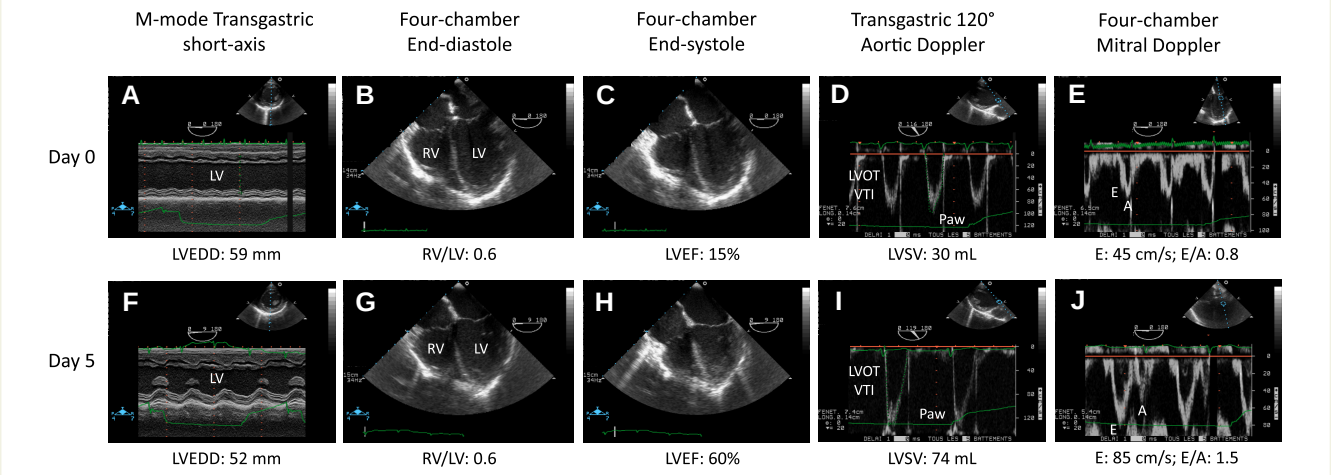

Figure 2 Main characteristics of SICM depicted by echocardiography in the early phase of septic shock and during recovery. This transesophageal echocardiography assessment was performed in a 14-year-old patient suffering from severe septic shock (i) upon ICU admission (Day 0) after 4 L of fluid resuscitation and high-dose vasopressor support had been required to stabilize blood pressure, and (ii) on Day 5, after successful recovery and during weaning from invasive mechanical ventilation. Findings include left ventricular end-diastolic diameter that may be at the upper limit of normal in the short-axis transgastric view (*A*) and normal right ventricular size in the transesophageal four-chamber view (*B*), severely depressed left ventricular systolic function (*C*) resulting in a decreased left ventricular stroke volume (*D*), and a mitral Doppler inflow pattern consistent with low left-sided filling pressures (*E*). These abnormal findings fully regressed after successful management of septic shock (lower panels, *F* to *I*). The mitral Doppler profile was normal in this young patient with normal left ventricular diastolic function (*J*). LV, left ventricle; LVED, left ventricular end-diastolic diameter; LVEF, left ventricular ejection fraction; LVSV, left ventricular stroke volume; RV, right ventricle

of associated SICM.[91–93] Elevated troponin is associated with an increased risk of death in sepsis.[94]

Right heart catheterization (RHC) provides a complementary assessment of the hemodynamic profile and is particularly useful for indicating the risk of pulmonary edema through the pulmonary artery occlusion pressure, but it may be limited by several factors in this specific setting including sources of error in cardiac output measurement, low LV filling pressures and indirect diagnosis of RV failure.[19] Transpulmonary thermodilution provides a continuous averaged measurement of cardiac output and stroke volume variation (a dynamic index of fluid responsiveness), but is heavily dependent on systemic vascular resistance and requires frequent recalibration.[95] Moreover, it shares the same limitations as RHC for the measurement of low cardiac index and identification of RV failure.[96] Overall, echocardiography is currently the cornerstone of assessing SICM at the bedside, identifying temporal variations in hemodynamic profiles, and assessing the response to therapeutic interventions. Main relevant echocardiography parameters aim at assessing fluid responsiveness,[97–103] LV systolic and diastolic function, and RV function are shown in *Table 1*. Lung ultrasound may be performed serially to detect the development of lung edema, assessed as increasing numbers of B-lines during fluid resuscitation.[19] Other imaging modalities such as magnetic resonance imaging or assessment of cardiac contractility using pressure-volume loop analysis cannot be used routinely in critically ill patients.

Finally, when should unstable coronary disease be considered as a differential diagnosis? Of 637 consecutive patients with confirmed acute myocardial infarction (AMI), 59 of 96 (61%) patients admitted initially for a non-cardiac disease had sepsis or septic shock.[104] Whether sepsis increases the risk of acute coronary syndrome remains unknown as traditional diagnostic criteria (electrocardiographic changes, regional wall motion abnormalities and elevated troponin) lack specificity.[105] Accordingly, clinical management of such patients should rely on individual risk factors, a thorough diagnostic work-up, and a benefit-risk assessment of interventions such as anticoagulation or antiplatelet therapy Of note, patients who survive sepsis have an increased risk of long-term cardiovascular events.[105]

Cardiovascular phenotypes

SICM may present with various hemodynamic profiles according to the timing and modality of assessment, the response to initial therapy, and any underlying host comorbidity such as a chronic cardiomyopathy.[13–17] Five cardiovascular phenotypes (LV systolic dysfunction, hyperkinetic profile, RV failure, persistent hypovolemia, and unremarkable central hemodynamics i.e. none of the above) were identified from a cluster analysis of clinical and transesophageal echocardiographic parameters recorded in 360 mechanically ventilated patients within 24 h of ICU admission for septic shock, but after fluid loading and initiation of vasopressor support.[13] The prevalence of these cardiovascular phenotypes was similar, ranging from 17% to 23% (see ESM S2, Supplementary data online, *Table S2*). Patients with LV systolic dysfunction had a lower cardiac index related to a diminished stroke volume and lower LVEF. Of note, these patients showed no signs of fluid responsiveness despite a low LV filling pressure (median E/E′ < 8). Compared with other cardiovascular clusters, patients with a hyperkinetic profile had a higher cardiac index, stroke volume and LVEF due to marked vasoplegia. Patients with RV failure had a markedly enlarged RV cavity (median RV/LV end-diastolic area: 0.8) with preserved LVEF and no evidence of fluid responsiveness. Despite a larger volume of fluid resuscitation prior to hemodynamic assessment, patients with persisting hypovolemia still showed marked signs of fluid responsiveness with a low cardiac index despite an elevated LVEF. Dedicated criteria have been proposed for the diagnosis of each cardiovascular phenotype; although these have

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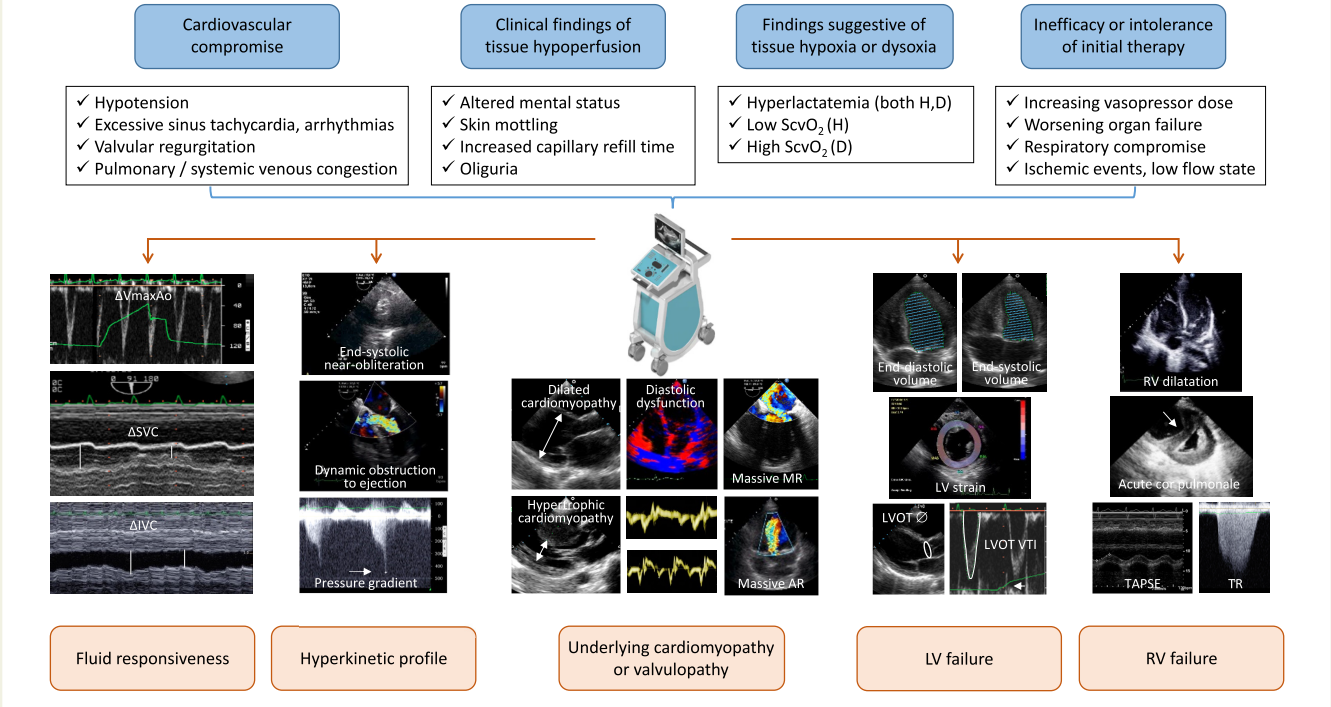

Figure 3 Proposed diagnostic work-up using hemodynamic assessment with critical care echocardiography. Sepsis-induced cardiovascular dysfunction may present as various hemodynamic profiles. Any clinical sign consistent with cardiovascular compromise, tissue hypoperfusion, tissue dysoxia, or inefficacy/intolerance to initial therapy should initiate prompt hemodynamic assessment. Transthoracic and/or transesophageal echocardiography provides detailed information to help guide therapeutic management (see text for details): for instance fluid challenge in the presence of fluid responsiveness, vasopressor support and avoidance of hypovolaemia for a hyperkinetic profile, administration of inotropes for left ventricular failure, or therapeutic strategies aimed at reducing pulmonary vascular resistance in patients with right ventricular failure secondary to excessive afterload. Echocardiography can also detect an underlying cardiomyopathy or valvulopathy exacerbated by sepsis, or which may be the cause of septic shock in the case of acute infective endocarditis. AR, aortic regurgitation; LV, left ventricle; LVOT, left ventricular outflow tract; MR, mitral regurgitation; RV, right ventricle; $ScvO_2$, central venous oxygen saturation; SvO_2, mixed venous oxygen saturation; TAPSE, tricuspid annular plane systolic excursion; TR, tricuspid regurgitation; VTI, velocity-time integral; ΔIVC, respiratory variations of the inferior vena cava diameter; ΔSCV, respiratory variations of the superior vena cava diameter; ΔVmaxAo, respiratory variations of maximal aortic Doppler velocity

high specificity, sensitivity is rather low.[13] Only 17% of patients exhibited an 'unremarkable' hemodynamic profile, with none of the above-described abnormalities (see ESM *S2*, Supplementary data online, *Table S2*). An important challenge is to distinguish adaptive myocardial mechanisms from pathological consequences leading to tissue hypoperfusion.[3]

Management

No evidence-based guidelines currently exist for the management of SICM. Although LV filling pressure remains typically normal or low at the initial phase of SICM, fluid resuscitation is best guided by serial assessment of fluid responsiveness. Fluid responsiveness can be defined as a significant increase of cardiac output (typically ≥10%–15%) following a fluid challenge (rapid infusion of 300–500 mL of fluid).[106] Prediction of fluid responsiveness aims at identifying the subset of patients who will significantly increase their cardiac output after a fluid challenge (responders), hence potentially avoiding detrimental fluid administration in non-responders with the risk of inducing volume overload and a positive fluid balance that is independently associated with mortality in septic shock patients.[107] Identification of responders without infusing a fluid bolus using 'dynamic' indices has been described. These use heart-lung interactions or a transient increase of venous return induced by passive leg raising to mimic a fluid challenge.[97–103,106,108] (*Table 1*). Patients with marked vasoplegia and a hyperkinetic heart, sometimes with an associated dynamic LV outflow tract obstruction, typically present with features of persisting hypovolemia.[109] Vasopressin, a pure vasoconstrictor, could advantageously be used here to reduce the dose of norepinephrine and, in turn, mitigate its inotropic effects that could contribute to LV outflow tract obstruction.[110] Patients with RV failure should be identified early to minimize any additional burden from suboptimal ventilator settings, and to detect false positive results from a marked pulse pressure variation that could erroneously suggest fluid responsiveness.[111] In these patients, a large pulse pressure variation results from cyclical RV afterload induced by tidal ventilation rather than cyclical reductions of venous return.

Dobutamine administration has been proposed for patients with persisting signs of tissue hypoperfusion and cardiac dysfunction despite adequate fluid loading and stabilisation of hemodynamics with vasopressor support (weak recommendation, low quality of evidence).[5] Low-dose dobutamine (e.g. 5 μg/kg/min) increased LV stroke volume in patients with SICM and persistent signs of tissue

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Table 1 **Main parameters routinely used to characterize the cardiovascular phenotype of septic cardiomyopathy using echocardiography**

Parameters	Thresholds	Value	Limitations	Comments
Assessment of fluid responsiveness				
Respiratory variations of maximal LVOT velocity	≥10% ≥ 18% provides 90% specificity[96]	Reproducibility	Requires mandatory MV and sinus rhythm False positives if RV failure Less accurate if low tidal volume and lung compliance	Mirrors pulse pressure variation monitored by an arterial catheter
Respiratory variations of superior vena cava diameter	≥21% ≥ 31% provides 90% specificity[96]	Remains valid if non-sinus rhythm No false positives if RV failure	Requires mandatory MV and transesophageal echocardiography	Measurement of the index of collapsibility
Respiratory variations of inferior vena cava	≥8% ≥ 18% provides 90% specificity in ventilated patients[96] ≥ 40 or ≥48% of collapse in spontaneously breathing patients[97,98]	Easy to obtain Remains valid if non-sinus rhythm Can be used in spontaneously breathing patients	Inaccurate if RV failure or increased IAP	Measurement of the distensibility index in ventilated patients Measurement of inspiration-induced collapse in spontaneously breathing patients Least accurate dynamic index in ventilated patients
Variations of LVOT velocity-time integral during passive leg raising	≥10% during passive leg raising in ventilated patients[99] ≥ 12% during passive leg raising in spontaneously breathing patients[100,101]	Leg raising mimics ≈300 mL fluid loading (transient effect) Can be used in spontaneously breathing patients	Contra-indications to passive leg raising False negative results if increased IAP	Maximal effect of transient increase in venous return expected within the first minute
Left ventricular systolic function				
LV ejection fraction	<50% or ≤ 40% according to definitions[67,68,77]	High feasibility Allows rapid assessment (eye-balling) Reproducibility	Highly influenced by loading conditions[14]	Fails to reflect myocardial contractility Reflects LV/aortic coupling
LV fractional area change	<45%	Can be used as a surrogate of LVEF[67,68]	LV apex is not assessed	Reflects perfusion territories of main coronary arteries
Mitral annular plane systolic excursion	<1.2 cm[67]	Feasible despite suboptimal two-dimensional imaging quality	Angle-dependency Only assesses longitudinal shortening Not valid if RWMA	Few validation studies
Tissue Doppler imaging Maximal systolic velocity at the mitral annulus (s′)	Septal mitral annulus <8.1 cm/s Lateral mitral annulus <10.2 cm/s Averaged value <9.2 cm/s[67]		Angle-dependency Only assesses longitudinal shortening Not valid if RWMA	Few validation studies
Global longitudinal strain (speckle tracking)	<−20%[a67]	Angle-independent More sensitive than LVEF[67] Allows segmental assessment	Not universally available Highly dependent on two-dimensional	Global and regional index with higher sensitivity than conventional parameters of systolic function

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Table 1 *Continued*

Parameters	Thresholds	Value	Limitations	Comments
			imaging quality Vendor-dependent	
Left ventricular diastolic function				
Mitral E/A	<0.8 (low) > 2 (high)[79]	Global index grossly reflecting left ventricular filling pressure Highly reproducible	Influenced by various factors unrelated to left ventricular diastolic function	Takes into account variables influencing cardiac load (e.g, volemia)
Mitral septal e′	<7 cm/s[79]	Feasible despite suboptimal two-dimensional imaging quality Reproducible	Angle-dependency Influenced by preload variations Not valid if RWMA	Cardiology diagnostic criteria not adapted to ICU patients[80,81]
Mitral lateral e′	<10 cm/s[79]	Feasible despite suboptimal two-dimensional imaging quality Reproducible	Angle-dependency Not valid if RWMA	Cardiology diagnostic criteria not adapted to ICU patients[80,81] Less sensitive to preload variations[79–81]
Averaged E/e′	>14[79]	Easily obtained surrogate of LV filling pressure	Intermediate values (8–13) do not permit precise evaluation of LV filling pressure	Cardiology diagnostic criteria not adapted to ICU patients[80,81]
Right ventricular function				
Tricuspid annular plane systolic excursion	<17 mm[67]	Feasible despite suboptimal two-dimensional imaging quality	Only assesses longitudinal shortening	Preserved despite (severe) RV pressure overload
Tricuspid systolic lateral annular velocity s′	<9.5 cm/s[67]	Feasible despite suboptimal two-dimensional imaging quality	Angle-dependency Only assesses longitudinal shortening	Few validation studies
RV fractional area change	<35%[67]	More representative of circumferential shortening	Requires clear depiction of free wall (anisotropy)	Large range of normal values
RV dilatation	Right/left ventricular end-diastolic area >0.6[67]	High feasibility Allows rapid assessment (eye-balling) Largely validated	Early (sensitive) marker of RV impairment (afterload, contractility defect)	Indicator of RV/pulmonary artery uncoupling

IAP, intra-abdominal pressure; ICU, intensive care unit; LV, left ventricle; LVEF, left ventricular ejection fraction; LVOT, left ventricular outflow tract; MV, mechanical ventilation; RWMA, regional wall motion abnormality; RV, right ventricle.
[a]Normal values are negative.

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hypoperfusion[16,18,112] (see ESM *S3*). A randomized controlled trial is currently evaluating the effect of dobutamine vs placebo on organ dysfunction in septic shock patients with associated LV systolic dysfunction and reduced stroke volume (NCT04166331). However, as increased catecholamines (endogenous and exogenous) have deleterious effects in septic patients,[113] non-adrenergic agents may be of interest. Levosimendan, a calcium-sensitizing inodilator, failed to provide any benefit on patient-centered outcomes[114–117] (see ESM *S3*). Accordingly, current Surviving Sepsis Campaign guidelines suggest against using levosimendan in septic shock patients with persistent hypoperfusion and cardiac dysfunction.[5] Studies are lacking on other inotropes such as the phosphodiesterase-3 inhibitor, milrinone.[118]

Other sepsis-induced organ failures are often interdependent, especially in the presence of cardiovascular dysfunction which reduces systemic blood flow and potentially exacerbates tissue hypoxia.[119] Strategies aimed at maximising oxygen delivery by increasing cardiac output to 'supranormal' levels (cardiac index >4.5 L/min/m^2) failed to improve outcomes.[120,121] Similarly, a strategy based on administration of fluid (including blood transfusion if hemoglobin levels were low) and dobutamine ('early goal-directed therapy') to increase central venous oxygen saturation ≥70%[122–124] also failed to confirm initial reports of improved outcomes when commenced within the first 6 h of hospital admission.[125]

Sinus tachycardia and arrythmias increase myocardial oxygen consumption and may potentially contribute to sepsis-induced LV systolic and diastolic dysfunction.[126] This constitutes a rationale for controlling heart rate in patients with SICM using short-acting beta-blockers (see ESM *S3*). Initial results[127,128] were not, however, confirmed by subsequent studies.[129–131]

Ivabradine, a selective inhibitor of I*f* channels in the sinoatrial node, acts as a bradycardic agent with preservation of blood pressure, cardiac output, and left ventricular systolic function.[132] However, a randomized controlled trial evaluating the effect of ivabradine vs. placebo in 70 patients with septic shock reported no benefit from this medication.[133]

Of note, these trials failed to determine the cardiovascular phenotype of septic shock patients at the time of screening. This emphasizes the need to tailor therapy according to documented hemodynamic profile.[134] Early veno-arterial ECMO could be considered in highly selected refractory septic shock patients with a low cardiac output syndrome and normal or elevated vascular resistance.[135]

Finally, AMI and SICM can co-exist. Managing patients with both conditions requires a careful balance between treating ischemic heart disease and addressing sepsis-related myocardial dysfunction. It is likely that septic patients may fulfil the 4th definition of myocardial infarction without having manifest occlusive disease. The prevalence and distribution of acute myocardial injury, Type 1 and Type 2 myocardial infarction in sepsis and related outcomes remains a knowledge gap. Although SICM is associated with troponin elevations that are prognostically relevant,[38,89,90,94] this finding should be interpreted with caution. Key management strategies include early recognition, prompt reperfusion therapy for AMI, fluid resuscitation for sepsis, and hemodynamic support.[136] Caution is essential when using AMI medications due to their potential for increased side effects in sepsis patients. Early reperfusion therapy, either via PCI or thrombolysis, remains a cornerstone for AMI management, even in the presence of sepsis. Close monitoring is crucial to balance the risks of bleeding from antiplatelet and anticoagulant therapy with the need for reperfusion. While beta-blockers are beneficial in AMI, their use in septic patients with hypotension or low cardiac output is generally avoided.

Prognosis

Short-term prognosis of SICM

The prognostic value of various echocardiography parameters used to diagnose SICM has been assessed in numerous retrospective single-centre studies (see ESM *S4*, Supplementary data online, *Table S4*). A common limitation of virtually all of these studies is the lack of a premorbid comparator. Reversibility of SICM is an inherent limitation because of the competing risk of early death. Another potential limitation is to decide whether LV systolic dysfunction alone should be assessed, or if LV diastolic and RV dysfunction should also be considered.

Left ventricular systolic dysfunction

A meta-analysis found no relationship between low LVEF and survival from sepsis.[137] In contrast, an increased LVEF secondary to arterial vasoplegia (reduced afterload) was associated with increased hospital mortality,[138] including those with an associated dynamic LV obstruction.[107] The relationship between LVEF and outcome in patients with sepsis and septic shock is complex and likely non-linear.[14,138] Specifically, higher mortality was recently observed in patients requiring high-dose norepinephrine (>0.5 μg/kg/min) with extreme values of LVEF (<25% and >70%).[138]

LV longitudinal strain could be a more sensitive indicator of LV systolic dysfunction than LVEF, but its routine use is limited by off-line analysis and often poor feasibility in ICU patients.[139,140] A recent meta-analysis found that LV global longitudinal strain was associated with both short- and mid-term mortality.[139] Mitral annular plane systolic excursion was independently associated with mortality[141] and myocardial injury.[142] However, studies evaluating the relationship between maximal systolic myocardial velocity measured by tissue Doppler imaging at the mitral valve annulus (s') and mortality yielded discordant results.[143,144] Overall, current data suggest greater prognostic value from distance-based but not velocity-based measurements of LV longitudinal contractility in septic patients.

Right ventricular dysfunction

Studies assessing the prognostic value of RV involvement in patients with septic shock have yielded conflicting results.[145–149] A recent meta-analysis of 1373 patients (82% with septic shock) found that RV dysfunction (albeit variably defined) was associated with mortality.[149] RV free wall strain was a more sensitive indicator of systolic dysfunction compared with more traditional parameters such as tricuspid annular plane systolic excursion, tricuspid valve systolic motion velocity and RV fractional area change, and was associated with mortality risk.[150] The presence of acute cor pulmonale was found in 22% of patients with ARDS and sepsis and was independently associated with 28-day mortality.[151] Prospective, well-adjusted prognostic studies are still scarce. The role of RV abnormalities and interaction with LV function, lung function and positive pressure ventilation remain important knowledge gaps.

Left ventricular diastolic dysfunction

Numerous studies suggest that LV diastolic dysfunction is prognostic for patients with sepsis and septic shock.[152–155] However, heterogeneity of defining criteria and time of assessment likely explain why some studies could find no relationship between LV diastolic properties and mortality.[156,157] Thus, no robust conclusion can be drawn at present regarding the potential prognostic

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Table 2 Current gaps of knowledge and future directions regarding SICM

Topics	Current situation	Future directions
Recognized criteria	• Use of variable diagnostic criteria preclude comparability of epidemiological studies and interpretation of interventional trials	• Establishment of a consensus definition and criteria (with regular updates) • Diagnostic criteria should be readily and broadly accessible
Epidemiological characterization	• Few large-scale epidemiological studies • Uncertain influence of underlying cardiovascular disease on SICM development and outcomes • Uncertain influence of SICM on long-term cardiovascular function and outcomes • Poorly characterized longitudinal assessment of cardiovascular phenotypes	• Development of large databases for prospective recording of clinical, physiological, imaging, biological characteristics and biobanking • Design of prospective studies describing the evolution of cardiovascular phenotypes during ICU/hospital stay (and impact of interventions) • Initiation of longitudinal studies focusing on long-term patient-centered outcomes
Prognostication	• Most prognostication studies are single-centre and underpowered • Adjustment on well-established prognosticators frequently lacking • Information on early course of SICM and vascular dysfunction not yet incorporated within prognostication studies	• Multicenter prospective large-scale studies using standardized echocardiography assessment and follow-up • Analysis taking into account temporal aspects of qualitative/quantitative indices (dynamic models) • Determination of evolution of cardiovascular phenotypes associated with poor outcome • Use of artificial intelligence for data analysis (causal machine learning)
Patient phenotyping	• Sepsis and septic shock are heterogeneous entities • Different phenotypes described using varied approaches (e.g. clinical, transcriptomic, proteomic) to identify patient subsets	• Validation of specific hemodynamic criteria to determine cardiovascular phenotypes • Identification of different biological signatures: inflammatory, immune and cardiac biomarker profiling allied to phenotype • Development of companion diagnostics and theranostics • Determination of various subpopulations of interest for potential targeted therapeutic interventions • Use of representative, long-term animal models to dissect pathophysiological mechanisms and test novel interventions
Personalized interventions	• Most trials test therapeutic interventions in broad sepsis populations • Current criteria for sepsis and septic shock encompass a wide range of patients with various profiles • Trials have mostly tested 'conventional' cardiovascular drugs	• Personalized interventions (assisted by causal machine learning) • Homogeneous subpopulations targeted to test specific interventions • Predictive or prognostic enrichment trial designs to improve chance of positive trial result • Anticipate predefined subgroup/sensitivity analyses (rather than *post hoc*) • Test new approaches derived from translational studies (e.g. peptides, monoclonal antibodies with cardiac or vascular effects)
Early identification	• Diagnosis of sepsis/septic shock frequently delayed • Diagnosis of SICM often delayed/not made • Delay in treatment increases mortality	• Broader use of imaging, wireless monitoring and point-of-care/rapid lab diagnostics • Artificial intelligence to generate risk scores and early warning alarms • Modify organisational structure to facilitate prompt guideline-driven management (e.g. outreach team)

SICM, sepsis-induced cardiomyopathy.

value of LV diastolic dysfunction. Future prospective studies should also take into account the confounding impact of pre-existing cardiac disease.

Long-term consequences

In large population studies, worse long-term cardiovascular outcomes have been reported among survivors of sepsis.[105,158–161] In a single-centre retrospective study, high-sensitive cardiac troponin T value sampled within 48 h of sepsis onset independently predicted 1-year mortality in survivors.[158] Potentially, such patients could benefit from out-patient investigation and follow-up.

In a retrospective study, survivors of sepsis with pre-existing cardiovascular comorbidities were at increased risk of major adverse cardiovascular events with a U-shaped association with LV contractility, as reflected by LV global longitudinal strain.[140] This relationship was not seen in patients without pre-existing cardiovascular comorbidities.

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Although SICM is usually described as reversible, patients with MRI patterns suggestive of residual myocardial edema and subepicardial remodelling at Day 28 and Day 49 have been reported.[162]

Current gaps of knowledge and future directions regarding SICM

Although there is solid evidence that the presence of SICM is a relevant contributor to organ dysfunction, remaining knowledge gaps merit further investigation, in particular how, when and in whom to intervene with a view to improving patient outcomes (*Table 2*). Like sepsis, SICM is a heterogeneous entity that needs better characterization using consensus-driven standardized criteria that must be rapidly and broadly accessible. Large cloud-based databases containing clinical, physiological, biological and imaging information, ideally augmented by sample biobanking, will both facilitate and accelerate this process. Such observational patient studies should be complemented by representative animal models to both discern pathophysiological mechanisms and test novel interventions (*Graphical abstract*).

These important steps will enhance epidemiology, including a greater appreciation of risk factors and short- and long-term outcomes, as well as the assessment of the temporal evolution of SICM, of the impact of interventions and long-term outcomes. Such knowledge, with cardiovascular and molecular phenotyping, will aid identification of patient subsets that would favorably respond both to conventional cardiovascular therapies (such as specific inotrope classes) as well as 'biologics' that target underlying mechanistic pathways (e.g. inflammatory, bioenergetic).

Some intriguing possibilities are being advanced, such as anti-inflammatory therapies,[163] cholesterol supplementation[40] and plasma exchange.[164] Rapid molecular diagnostics and theranostics, increasing availability of high-end yet more affordable bedside imaging, and supported by artificial intelligence, will augment these efforts.[165,166] This collective knowledge will inform trial design, including predictive and prognostic enrichment, and enhance the probability of finding outcome benefits.[167,168]

Conclusion

Since its first description in 1984, SICM has been shown to significantly contribute to the development of organ dysfunction in septic patients. Forty years on, there have been considerable improvements in our understanding of the pathophysiology and facilitated access to bedside diagnosis with a greater in-depth description of its varying modes of clinical presentation. Many questions remain, but these are being identified and addressed and, with the aid of improved technology, will result in personalized therapies that improve both short- and long-term outcomes.

What was the patient's course?

The patient required norepinephrine at doses up to 0.8 µg/kg/min and invasive mechanical ventilation due to pneumonia-induced severe hypoxemia. A rapid test for S. pneumoniae antigen was positive and appropriately targeted antimicrobial therapy was commenced. The patient spent 9 days in the ICU. Echocardiography at discharge showed a total recovery of LV systolic function with normal ejection fraction.

Supplementary data

Supplementary data are available at *European Heart Journal* online.

Declarations

Disclosure of Interest

All authors declare no disclosure of interest for this contribution.

Data Availability

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